

## Enhanced Frequency Domain Analysis Replaces Older Heart Rate Variability Methods

A. I. Vinik, MD; B. Aysin, PhD; and J. Colombo, PhD

**BACKGROUND:** Enhanced frequency domain (fd) analysis (EFDA) of heart rate variability (HRV) includes respiratory activity (RA) analysis. EFDA is a means of non-invasively measuring the autonomic nervous system (ANS): both branches independently, simultaneously, and objectively (Fig. 1). EFDA completes older fdHRV methodologies to allow proper dissection of the ANS to further diagnostics. For example, Orthostatic Hypotension (OH) is common in Diabetics. OH is a failure of the sympathetic NS (SNS), but it could also be (partially) caused by an overdrive of the parasympathetic NS (PSNS). Either way it is not an ANS structural deficit, it is a functional issue. Identifying this difference can facilitate diagnosis and therapy.

**METHODS:** Two or more ANS tests were performed on 389 adult diabetic patients. The average age of the cohort is 63.2 (range is from 25 to 96), with 161 females. The cohort includes 354 NIDDM (average age 63.5) patients and 35 IDDM patients (average age 61.1).

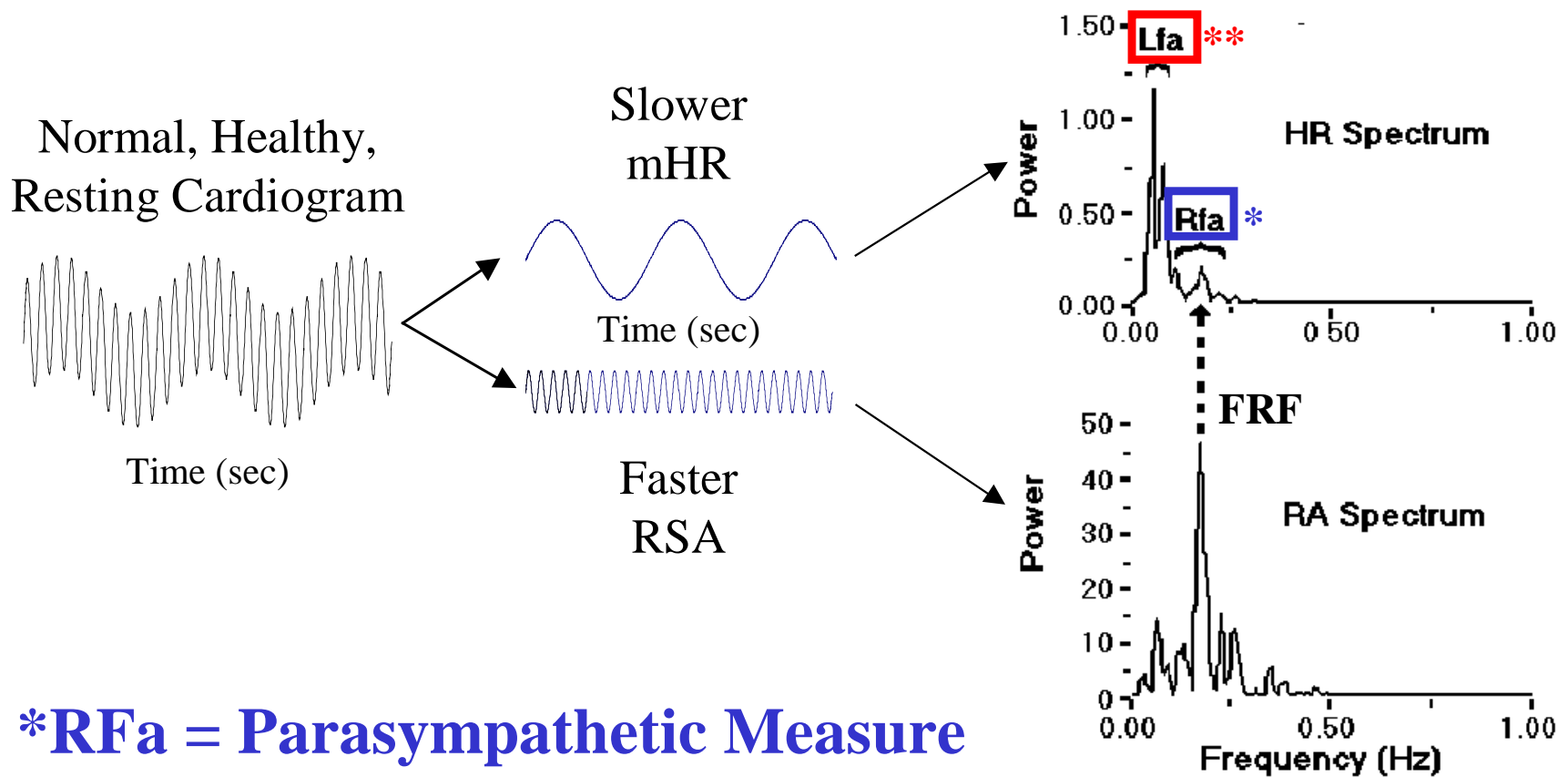
Table 1: Population Age Data

Age Range	Numbers	Average Age	Females
< 31	2	26.5	1
31 to 40	15	35.9	7
41 to 50	43	45.6	21
51 to 60	84	56.0	30
61 to 70	79	66.3	35
71 to 80	113	75.0	53
> 81	24	83.4	13

The data collected included patient's EKG (digitized at 250 Hz), respiratory activity (digitized at 60 Hz), and blood pressure. These data were collected from a clinical study that includes a resting baseline; periods of deep (relaxed) breathing, short Valsalva maneuvers, and quick stand immediately followed by quiet standing. The study challenges were separated by periods of rest to allow the patient's ANS to return to baseline.

From these data, the patient's fdHRV (LF, HF, and L/H) and EDFA (LFa, RFa, and LFa/RFa) parameters were computed in response to clinical challenges, and at rest. Patients presenting with SNS withdrawal (suggesting orthostasis) were analyzed by considering L/H and LFa. Also, patients presenting with paradoxical PSNS syndrome (PPS) were analyzed by considering HF and RFa. PPS is defined as an abnormal increase in PSNS activity in response to a SNS challenge (e.g., Valsalva or stand).

# HRV & RA = ANS



**\*Rfa = Parasympathetic Measure**

**\*\*Lfa = Sympathetic Measure**

**Lfa/Rfa = Sympathovagal Balance**

Figure 1

**RESULTS:** Comparisons between fdHRV parameters and EFDA parameters from OH patients, showed that LFa positively identified more patients than L/H (73% vs 29%,  $p < 0.001$ ). Of the 389, 43.7% presented with clinical OH symptoms. Similar comparisons between PPS patients showed that RFa identified more patients than HF (94% vs 18%,  $p < 0.001$ ). Of the 389, 67.3% presented with clinical symptoms of PPS. EFDA repeatability studies resulted in  $11.4\% \pm 1.3$  variability from test to test within a short period of time ( $< 6$  weeks).

The Bx ANS parameters from EFDA are quantitative measures of ANS function or activity. Poor ANS results have been correlated with poor outcomes and normal ANS results have been correlated with healthy outcomes [Shoemaker, *et al.*; Adiraju and Colombo (III)]. The Bx ANS results are also plotted in Figure 2 (the thicker solid lines with squares representing the Bx LFa, and the asterisks representing the Bx RFa). The normal ranges for both are 0.5 to 10.0  $\text{bpm}^2$ . For the case of this cohort, the Test 1 results (LFa =  $1.01 \text{ bpm}^2$  and RFa =  $0.97 \text{ bpm}^2$ ) are nearing the low end of the normal range. The Test 2 results show that, overall, the patients' ANS inputs to their hearts are weakening: The SNS measure (LFa) dropped to  $0.65 \text{ bpm}^2$  and the PSNS measure (RFa) dropped to  $0.70 \text{ bpm}^2$ . A Bx PSNS measure of  $0.1 \text{ bpm}^2$  is the mathematical equivalent to the Framingham Heart Study threshold for cardiac risk.

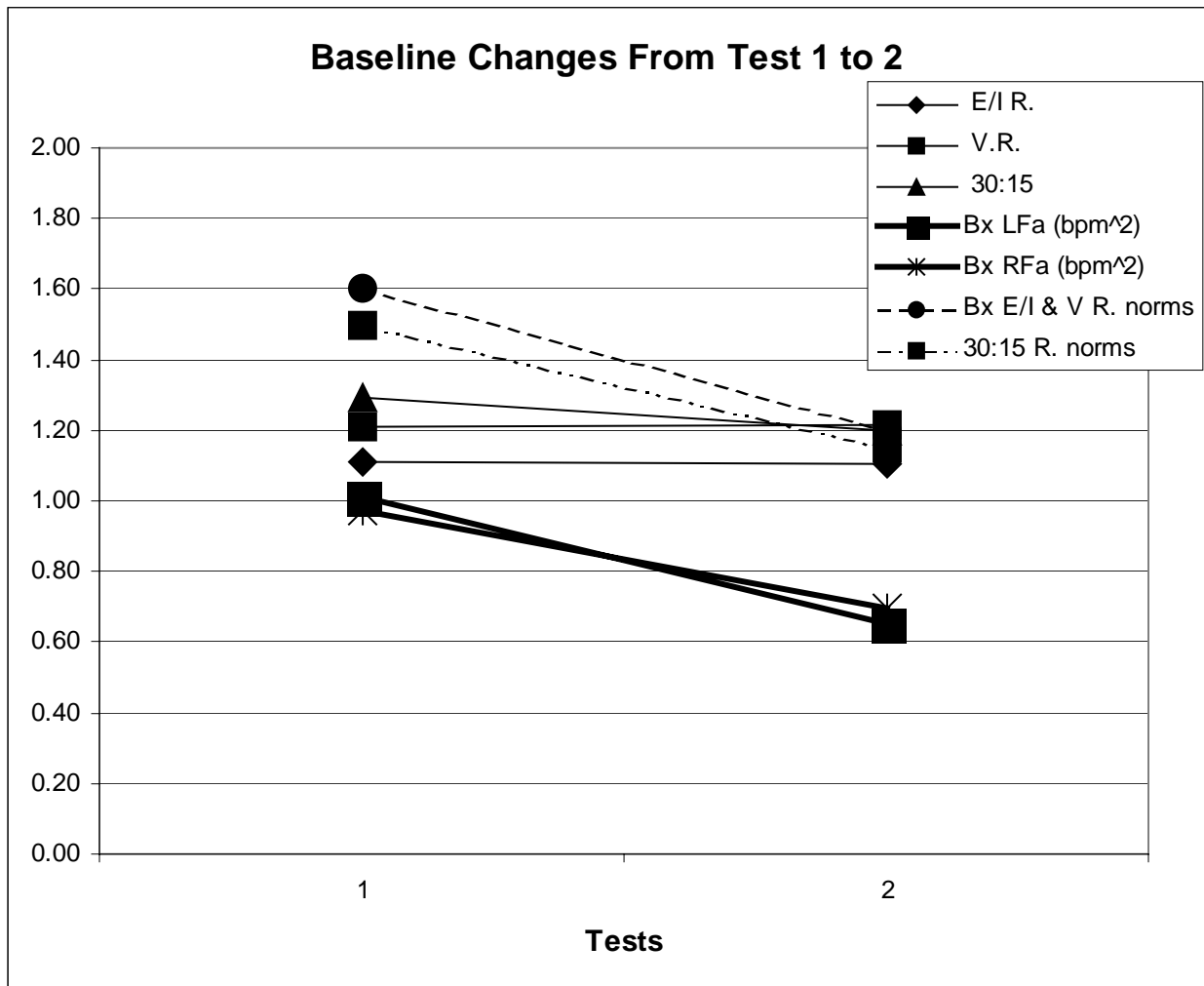


Figure 2

The dynamic nerve response to challenges can be a sensitive and a possible earlier indicator of systemic ANS dysfunction. Figures 3 and 4 compare the RFa and HF responses to deep breathing challenge and LFa and LF responses to Valsalva challenge, respectively. The frequency domain HRV results, by age, from the two tests are depicted by broken lines in the two figures. The ANS measure (RFa & LFa, respectively) results, by age, from the two tests are depicted by solid lines in the two figures. Assuming that the effects of diabetes accelerates the aging effects on the ANS, the decline in the patient's ANS responses to challenge (RFa to deep breathing and LFa to Valsalva) would be faster than that of age matched normals. The low end of the age-matched normal ranges are depicted by the thinner solid line in the two figures. The upper end of the age-matched normal range was omitted for clarity. Suffice it to say, that, even the younger patients' results are well within the upper range of the age-matched normal data. As seen in the two figures, the ANS measures for the younger portion of the population start out well above the low end of normal, but the older patients end up at or below the low end of normal.

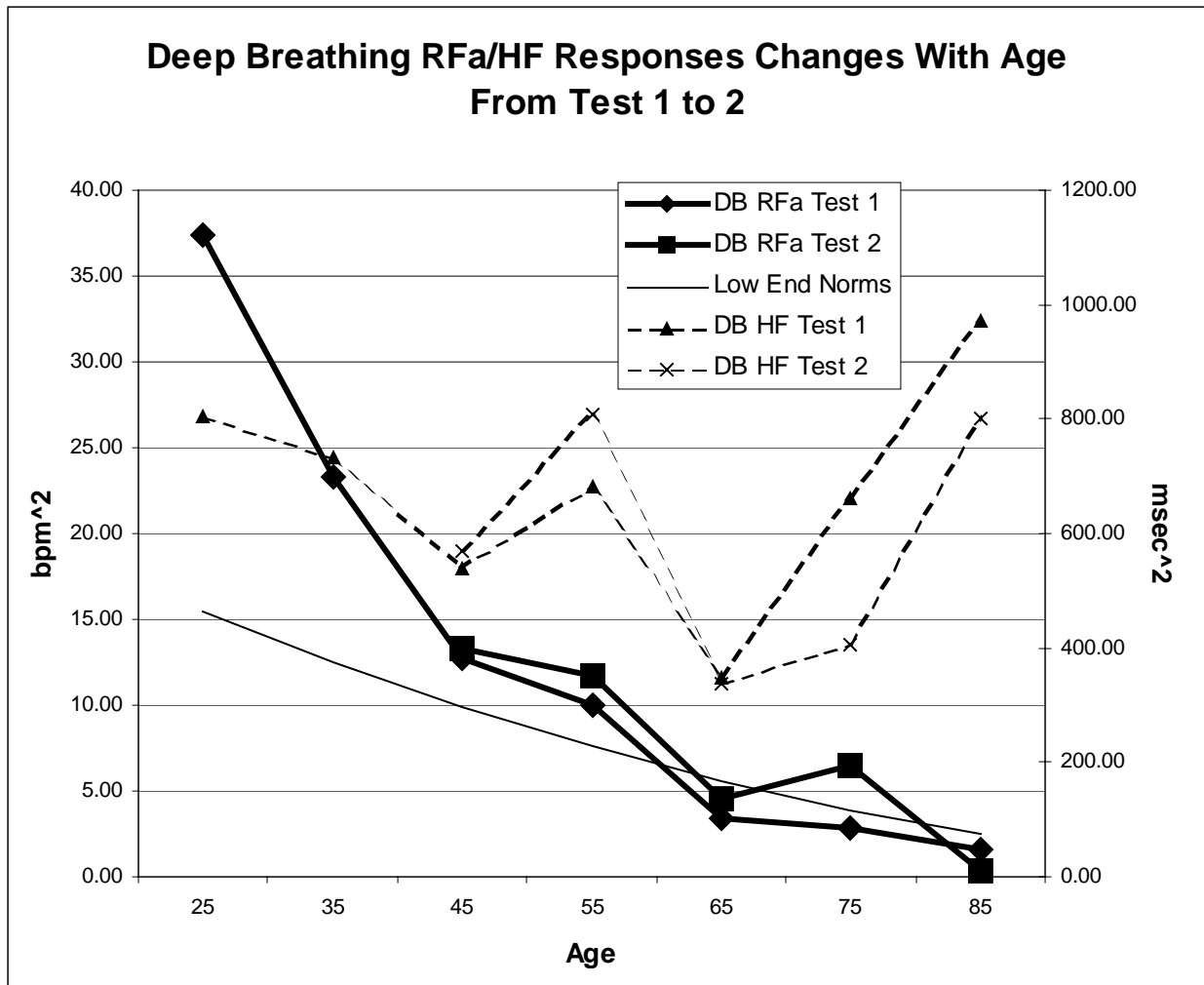


Figure 3

The fdHRV data for the HF (Fig. 3) seem to start to indicate a downward trend that is accelerating with age, but in both Tests, the trend reverses after age 65. This is not the case for

the fdHRV LF data (Fig. 4). The LF trend continues and, in Test 2, almost matches the results from the ANS measures. These results should not be surprising since the fdHRV method and the ANS method for computing LF and LFa, respectively, are similar. Where the ANS measure (EFDA) seems to be more beneficial, is in the younger population (theoretically the earlier stages of the disease) where it can provide earlier indications of ANS decline, while the fdHRV parameters are still relatively flat. This also seems to reduce the sensitivity of the frequency domain LF measure by forcing a steeper slope, inflating the rate of decline.

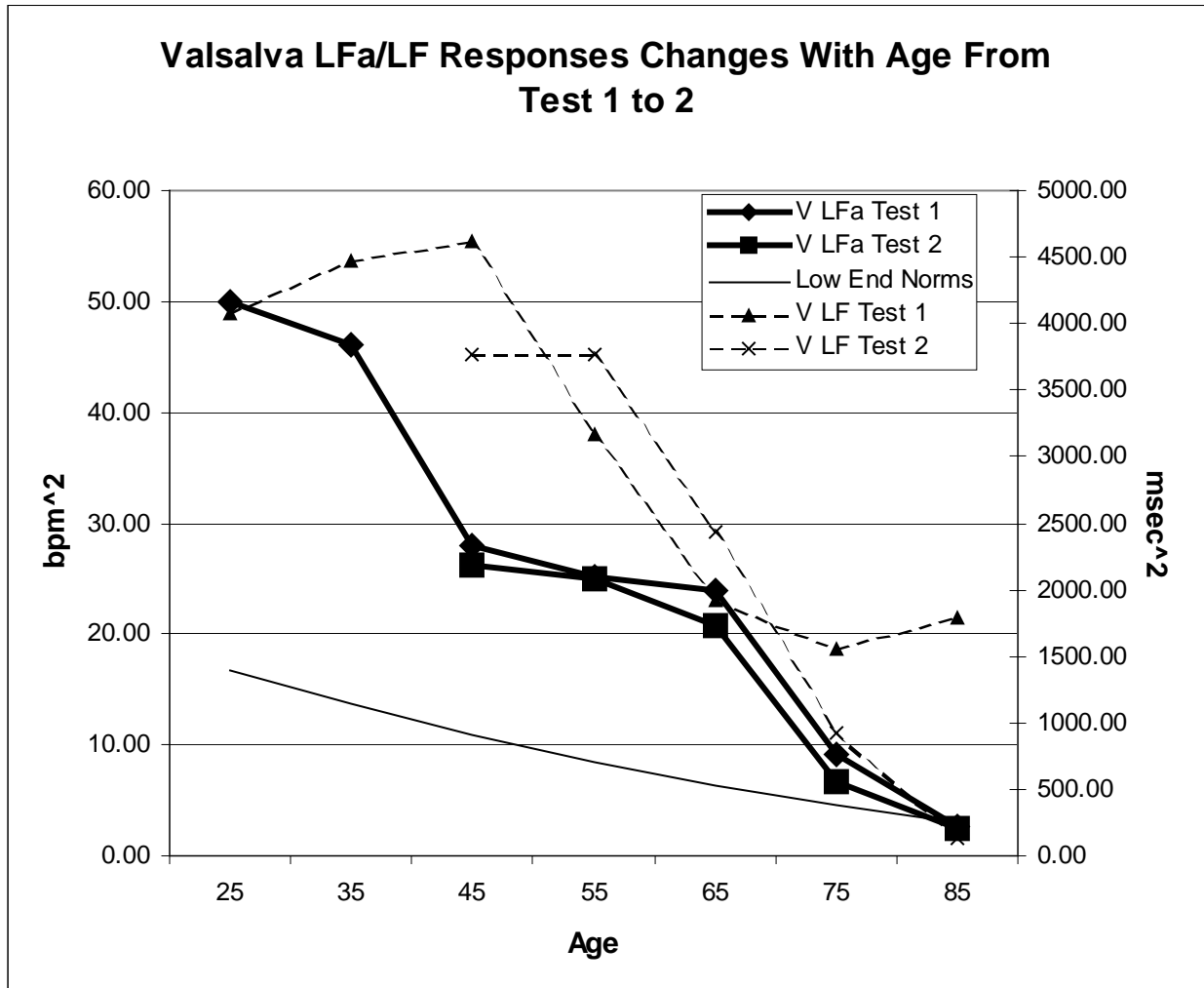


Figure 4

### ORTHOSTASIS INDICATIONS

FDHRV analysis utilizes the LF/HF ratio (L/H) as the indicator of a change in SNS activity level in response to a challenge. ANS monitoring (EFDA) uses the changes in the LFa as the indicator. Orthostasis is defined physiologically as SNS withdrawal upon postural change. Patients at risk for orthostasis can be quantitatively measured using either fdHRV or ANS profiling. A comparison of L/H and LFa was made within this patient population. The assumption is that a drop in either parameter in response to a postural change indicates SNS withdrawal. Of this patient population, 170 (43.7%) of the patients presented to their physicians with clinical symptoms of orthostasis. LFa identified more patients with orthostasis than L/H

(73% vs 29%,  $p < 0.001$ ). LFa identified more patients than physician diagnosis (73% vs 18%,  $p < 0.01$ ) and combination of diagnosis and symptoms (73% vs 35%,  $p < 0.002$ ). L/H identified more patients than physician diagnosis (25% vs 18%,  $p < 0.01$ ) but less compared to combination of diagnosis and symptoms (25% vs 35%,  $p < 0.01$ ). The LFa identified orthostasis more frequently than any decrease in BP (73% vs 56%), and more often than either a 20 mmHg or 10 mmHg decrease in systolic or diastolic BP, respectively (73% vs 16%). Overall the ANS parameter, LFa, identified orthostasis (as defined by sympathetic withdrawal) far better than either the fdHRV method or even the physician. In fact, the data suggests that the fdHRV method would result in a 44% false negative rate. These results are similar to those of Stoupakis *et al.*, [AHA Abstr., 2002].

## **PARADOXIC-PARASYMPATHETIC SYNDROME**

Paradoxical Parasympathetic Syndrome (PPS) is a syndrome that can be identified only through simultaneous measures of both ANS branches. PPS is defined as an abnormal increase in the PSNS in response to a SNS stimulus (Valsalva or postural change). For postural change (stand), PPS is defined as any increase in PSNS activity in response to the postural change. For Valsalva, since a quick breath is necessary to initiate the Valsalva, a doubling in the PSNS level is acceptable. A change of more than a doubling is considered abnormal (PPS). PPS seems to include a number of symptoms such as sleep disorders, restless leg syndrome, GI upset, frequent morning headaches or migraines, morning cognitive or memory difficulties, anxiety or depression, varicose veins, edema, poor circulation, and orthostasis. PPS also seems to destabilize patients' response to disease or therapy [Adiraju and Colombo (PPS)].

A comparison of HF and RFa was made within this patient population assuming an increase in either parameter in response to the Valsalva challenge or postural change indicates PPS. Of this patient population, 262 (67.3%) of the patients presented to their physicians with more than four of the clinical symptoms of PPS. RFa identified more patients with PPS than HF (94% vs 18%,  $p < 0.001$ ). In fact, the data suggests that the fdHRV method would result in a 76% false negative rate.

**DISCUSSION:** ANS monitoring (EFDA) uses the heart and lungs as a window to non-invasively view the ANS. The ANS is known as one of the great mediators of all of the body's metabolic needs on a moment-by-moment basis. Since the body only has one heart and one set of lungs, the ANS is forced into a continual compromise that requires a single heart rate and a single respiratory rate to suffice for all. By monitoring the compromise from the point of view of respirations and heart rate, an overall, systemic measure is made.

The data from Figure 2 suggest that the baseline or resting levels of ANS measures (EFDA) can be more sensitive than tdHRV measures in changes in patients' ANS health and neurocardiologic innervation. Although both indicators are low and the tdHRV parameters suggest that average patient in the cohort is near or in DAN, the time domain measures show little or no sensitivity to continuing ANS decline as compared to the ANS measures.

Assuming that the data in Figures 3 & 4 represent the trend for a single patient, these data could suggest that autonomic decline can be detected more sensitively, and potentially sooner. In fact, the delay in showing a decline in the fdHRV measure of LF may, in part, present as a false indication of better health or stasis of ANS decline leading both physician and patient to be less aggressive regarding the disease.

It is presumed that the differences between the fdHRV techniques and the EFDA-based ANS monitoring techniques are the reason for the high false negative rates. For the fdHRV, the LF is considered a mixed measure (SNS and PSNS). The HF is sometimes considered a PSNS measure when the breathing frequency is in the HF frequency range. Otherwise the HF term is merely a noise measure. The HF range is a relatively broad, fixed frequency range. The L/H ratio suffers from the same problem as the HF term. That is by inclusion, when the breathing frequency is not in the HF range what does the L/H mean.

Whereas, EFDA-based ANS monitoring uses the RA analysis to identify Vagal outflow which specifies PSNS influence on HRV, without extraneous frequency content and regardless of the breathing frequency. With a more specific measure of PSNS activity, a more specific measure of SNS activity can be computed. Thus the EFDA low frequency area (LFa) and respiratory frequency area (RFa) terms are more pure measures, and more highly correlated with SNS and PSNS activity; respectively.

When applied clinically, these terms allow proper dissection of the ANS to further diagnostics. The examples presented include OH and PPS. In both cases the ANS monitoring parameters provided indications of dysfunction with many fewer false negatives than fdHRV. Further, perhaps due to their sensitivity, the ANS monitoring parameters were perhaps earlier in detecting functional changes that may lead to clinical diagnoses.

**CONCLUSION:** EFDA, which includes analyses of RA, can provide physicians with a more sensitive, quantifiable measure of their patient's ANS levels of activity. Evidence suggests that these measures can also detect these changes sooner than other measures. This can be particularly useful, especially in light of recent data [Adiraju and Colombo (III) and (PPS)] that suggests that reversing poor ANS results can lead to improved outcomes, and that slowing ANS decline can prolong the quality of life (including the proper maintenance of GI motility and urogenital function), and possibly life expectancy.

The EFDA-based, ANS monitoring parameters have been shown to be reflective of medication effects as well as disease and aging effects [include all of Ansar's work]. Patient reactions to medication and therapy, either dosing or agent, can be directly monitored and used to guide outcomes. The fact that diabetes, as well as many other chronic, progressive diseases, tend to present with secondary symptoms over time, and given that these secondary symptoms can be of an autonomic nature (postural change difficulties, sleep difficulties, circulatory and vascular disorders, GI upset, etc.) suggests that a greater understanding of a particular patient's ANS response can be important. The patient's ANS response can provide the physician additional information to help enhance treatment and therapy.